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Synthesis of (−)-Isonitrin B

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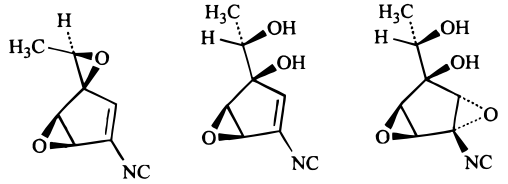
Abstract: The first enantioselective synthesis of (−)-isonitrin B (**2**), the parent of a small family of isonitrile antibiotics having compact but highly functionalized (and highly reactive) cyclopentane rings, is described. They key in this synthesis is the cyclization of **5b** to **4b**, by way of the intermediate alkylidene carbene.

Introduction

Isonitrin A (**1**), isonitrin B (**2**), and trichoviridin (also called isonitrin C) (**3**) are three representatives of a small family of isonitrile antibiotics[1] having compact but highly functionalized (and highly reactive) cyclopentane rings (eq 1). Compared with isonitrin B (**2**), isonitrin A (**1**) has an extra epoxide outside the cyclopentane ring, while trichoviridin (**3**) has an extra epoxide in the ring. The current rapid rise in bacterial infections that do

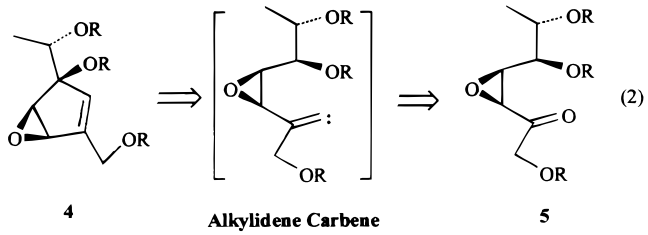


(1)

1 **2** **3**

not respond to antibiotic therapy makes it urgent that leads such as these be pursued. Although isonitrin B was first described more than 15 years ago, only one synthesis, by Baldwin of the racemate, has been reported.[2] Baldwin also accomplished the conversion of isonitrin B (**2**) to isonitrin A (**1**) and to trichoviridin (**3**).[3] We now report the first enantioselective synthesis of (−)-isonitrin B (**2**), the parent member of this family of antibiotics.

The conventional approach to the assembly of highly functionalized ring systems has been to first construct the ring(s) and then to elaborate the functional groups. We proposed to invert this strategy (eq 2), by first preparing the fully oxygenated ketone **5** and then cyclizing it to **4**. The essential question was



(2)

4 **Alkylidene Carbene** **5**

whether the generation and cyclization of the alkylidene carbene[4] from this highly functionalized substrate could proceed smoothly to form the strained bicyclic product **4**. The key to this analysis is the observation that intramolecular C−H insertion of an alkylidene carbene proceeds with retention of absolute configuration.[5]

[#] X-ray crystallography.

(1) For isolation and physiological activity, see: (a) Fujiwara, A.; Okuda, T.; Masuda, S.; Shiomi, Y.; Miyamoto, C.; Sekine, Y.; Tazoe, M.; Fujiware, M. *Agric. Biol. Chem.* **1982**, *46*, 1803. (b) Okuda, T.; Fujiwara, A., Fujiwara, M. *Agric. Biol. Chem.* **1982**, *46*, 1811.

(2) For the correction of the structure of isonitrin B and the only previous (racemic) synthesis, see: Baldwin, J. E.; Aldous, D. J.; Chan, C.; Harwood, L. M.; O'Neil, I. A.; Peach, J. M. *Synlett* **1989**, 9.

(3) For the conversion of isonitrin B to isonitrin A, see: (a) Baldwin, J. E.; O'Neil, I. A. *Synlett* **1990**, 603. For the conversion of an intermediate in the isonitrin B synthesis to trichoviridin, see: (b) Baldwin, J. E.; O'Neil, I.; Russell, A. T. *Synlett* **1991**, 551. (c) Baldwin, J. E.; Adlington, R. M.; O'Neil, I. A.; Russell, A. T.; Smith, M. L. *J. Chem. Soc., Chem. Commun.* **1996**, 41.

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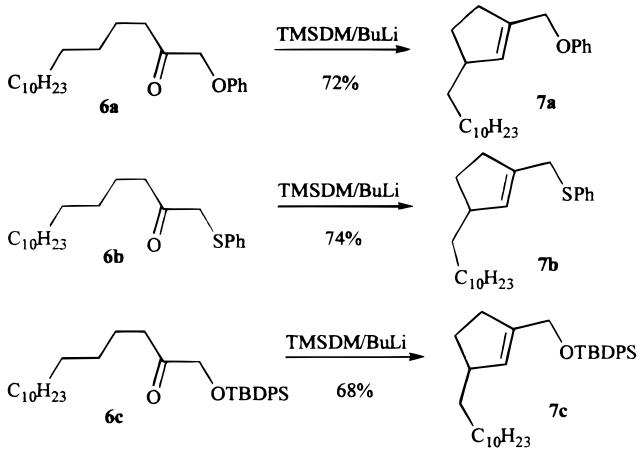
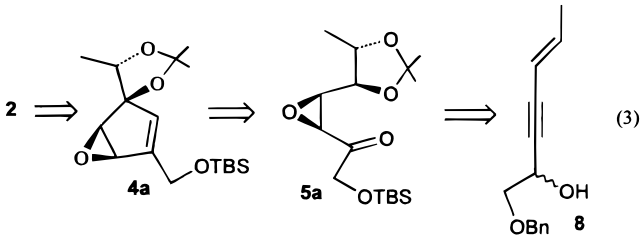
Scheme 1



Generation of Alkylidene Carbenes from α-Heterosubstituted Ketones. Before our investigation of the preparation and cyclization of the alkylidene carbene derived from ketone 5, we first addressed the simple question of whether an α-heterosubstituted ketone (**6a**−**6c**, Scheme 1) would participate efficiently in 1,5 C−H insertion.[6]

Several reagents have been used to convert ketones into the corresponding alkylidene carbenes.[4] In our hands, the most efficient protocol has been our modification[7] of the Ohira procedure.[8] Treatment of a DME solution of trimethylsilyldiazomethane with *n*-BuLi at −60 °C resulted in a suspension that was allowed to warm until just homogeneous. This solution of trimethylsilyldiazomethyllithium was chilled again to −40 °C before addition of ketones **6a**−**6c**. Under these conditions, insertion proceeded to give exclusively **7a**−**7c**.

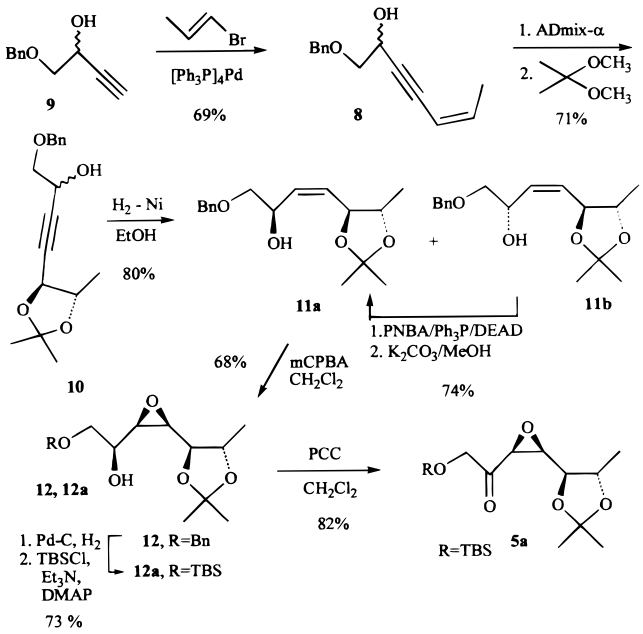
First-Generation Approach. Construction and Cyclization of the Acetonide-Protected Ketone 4a. In our first retrosynthetic analysis of (−)-isonitrin B (eq 3), the key intermediate was projected to be the acetonide-protected cyclopentene **4a**, which would be prepared from ketone **5a** by alkylidene carbene insertion. The cyclization precursor, ketone **5a**, was to be prepared from the racemic alcohol **8** over several steps.



(3)

We started (Scheme 2) our synthesis from alkyne **9**.[9] Coupling with trans 1-bromo-1-propene followed by enantioselective

Scheme 2



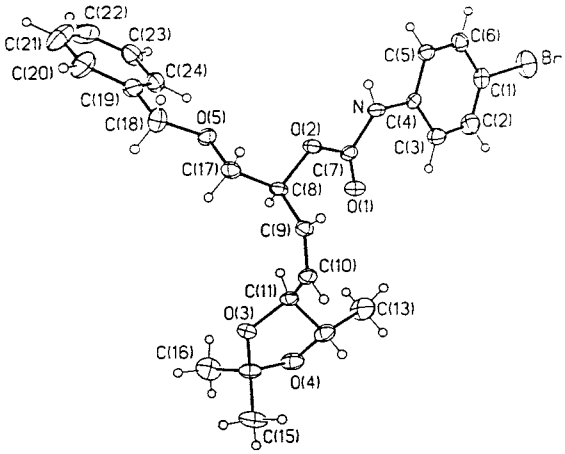


Figure 1. ORTEP of the 4-bromophenylurethane of **11b**. Thermal ellipsoids at 30% probability and the hydrogen atoms, with the exception of those on chiral carbon atoms, are omitted for clarity.

dihydroxylation[10] and protection led to the acetonide **10**. Hydrogenation[11] gave a pair of diastereomers, **11a** and **11b**, which were readily separable on silica gel. The relative configuration of **11b** was established by X-ray analysis of the derived 4-bromophenylurethane (Figure 1).[12] Mitsunobu inversion[13] of **11b** to **11a** proceeded smoothly. Threo-selective epoxidation (mCPBA) of **11a** gave the desired epoxide **12** as the expected major diastereomer.[14] We expected that the alkylidene carbene derived from **12** would insert both into the

(4) For reviews of cyclopentene construction by intramolecular C−H insertion of an alkylidene carbene, see: (a) Taber, D. F. *Methods of Organic Chemistry*; Helmchen, G., Ed.; Georg Thieme Verlag: Stuttgart, New York, 1995; Vol. E21, p 1127. (b) Kirmse, W. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1164.

(5) (a) Gilbert, J. C.; Giamalva, D. H.; Baze, M. E. *J. Org. Chem.* **1985**, *50*, 2557. (b) Ohira, S.; Moritani, M.; Ida, T.; Yamato, M. *J. Chem. Soc., Chem. Commun.* **1993**, 1299.

(6) After this phase of the work was completed, Ohira reported the facile cyclization of an α-hetero ketone: Ohira, S.; Sawamoto, T.; Yamato, M. *Tetrahedron Lett.* **1995**, *36*, 1537.

(7) Taber, D. F., Meagley, R. P. *Tetrahedron Lett.* **1994**, *35*, 8405.

(8) Ohira, S.; Okai, K.; Moritani, T. *J. Chem. Soc., Chem. Commun.* **1995**, *36*, 1537.

(9) Takano, S.; Sugihara, T.; Ogasawara, K. *Synlett* **1991**, 279.

(10) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.; Kwong, H.; Morikawa, K.; Wang, Z.; Xu, D.; Zhang, X. *J. Org. Chem.* **1992**, *57*, 2768. The crude diol from this procedure had an ee of 73%. A single crystallization raised the ee to 92%. The latter material was used in this synthesis. The assignment of the absolute configuration of the diol was based on literature precedent.

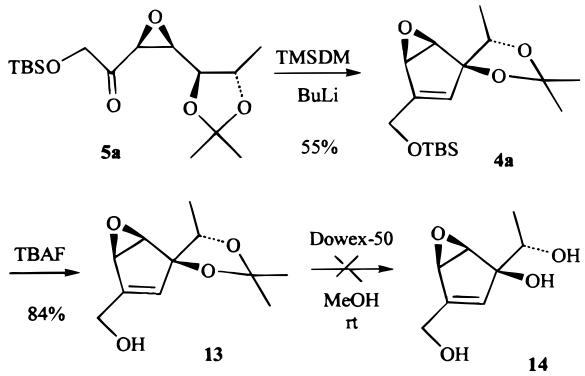
(11) (a) Brown, C. A.; Ahuja, V. K. *J. Org. Chem.* **1973**, *38*, 2226. (b) Brown, C. A.; Ahuja, V. K. *J. Chem. Soc., Chem. Commun.* **1973**, 553.

(12) Crystal data for the 4-bromophenylurethane of **11b**: $C_{24}H_{28}BrNO_5$, $P2_12_12_1$, a = 8.1279(3), b = 13.3495(5), and c = 22.1776(8) Å, V = 2406.35(15) Å^3, Z = 4, T = 203 K; $R(F)$ = 4.77%, $R(wF^2)$ = 9.46%.

(13) (a) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017. (b) Caine, D.; Kotian, P. L. *J. Org. Chem.* **1993**, *57*, 6587.

(14) Rossiter, B. E.; Verhoeven, T. R.; Sharpless, K. B. *Tetrahedron Lett.* **1979**, 4733.

Scheme 3

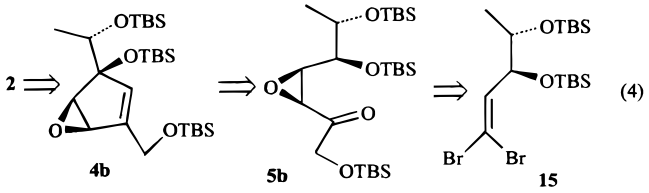


target methine group and the benzylic methylene group,[15] so the benzyl protecting group was replaced with a *tert*-butyldimethylsilyl group to give alcohol **12a**, which was oxidized to ketone **5a**.

With the results of the model study of the cyclization of the α-heterosubstituted ketones in hand, we were ready to attempt the cyclization of ketone **5a** (Scheme 3). The key question was whether the alkylidene carbene C−H insertion reaction would still be competent when there was an epoxide between the ketone and the target C−H bond. There were two concerns: the additional ring strain and the deactivation of the target C−H by the electron-withdrawing oxirane. In the event, we were delighted to observe that treatment of the ketone **5a** with the anion of (trimethylsilyl)diazomethane in DME gave the acetonide-protected cyclopentene **4a**. Removal of the silyl protecting group gave the primary alcohol **13**.

Alcohol **13** proved to be unstable, as had been expected. Since we would need to remove the acetonide group from the fragile cyclopentadiene monoepoxide at the end of the synthesis, we attempted this deprotection at the stage of alcohol **13**. Unfortunately, none of the deprotected triol **14** could be found.

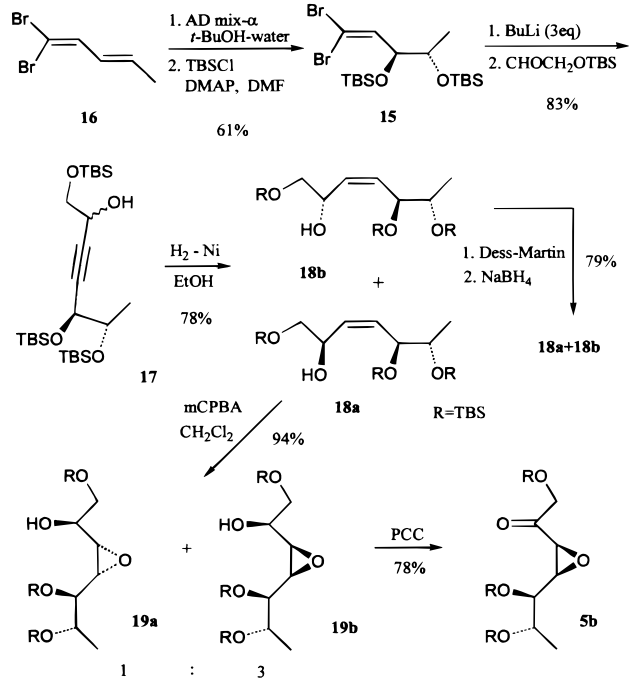
Second-Generation Approach. Synthesis of (−)-Isonitrin B. It was clear from the investigation in the acetonide series that we would have a greater chance of success if we were to prepare the tris-silylated ketone **5b** (eq 4). We proposed to synthesize ketone **5b** from the dibromide **15**.



(4)

The construction of the required cyclization precursor **5b** (Scheme 4) began with (*E*)-1,1-dibromo-*trans*-1,3-pentadiene (**16**), which was available in one step[16] from crotonaldehyde. Sharpless asymmetric dihydroxylation[10] of **16** followed by protection with *tert*-butyldimethylsilyl chloride resulted in dibromide **15**. The key to this approach would be the ability to separate the diastereomers resulting from the addition of the lithium acetylide derived from **15** to O=CH−CH_2−OTBS.[17] In the event, exposure of **15** to 3 equiv of *n*-BuLi[18] followed

Scheme 4



by addition of the aldehyde gave the coupling product **17** as an inseparable pair of diastereomers. Fortunately, hydrogenation[11] gave the corresponding *Z*-alkenes as a pair of diastereomers (**18a** and **18b**) that were readily separable on silica gel.

The relative configuration of the correct intermediate **18b** was established by chemical and spectroscopic correlation with alcohol **11a**, the structure of which had been secured by X-ray crystallography. The alcohol **18b** was recycled to the 1:1 mixture of **18a** and **18b** by Dess−Martin oxidation[19] followed by $NaBH_4$ reduction. The expected threo-selective epoxidation of **18a**[14] then gave the two diastereomeric epoxides **19a** and **19b** in a 1:3 ratio favoring the desired epoxide **19b**. Epoxide **19b** was oxidized efficiently to the cyclization precursor, ketone **5b**.

As before, treatment of the ketone **5b** with the anion of (trimethylsilyl)diazomethane in DME gave clean conversion to the cyclized product **4b** (Scheme 5). Selective deprotection of the primary silyl group of **4b** under the neutral conditions of HF/pyridine[20] gave the acid-sensitive cyclopentadiene monoepoxide **19**, which was converted to the aldehyde **20** by Dess−Martin oxidation[19] and was further oxidized to the acid with sodium chlorite.[21] Treatment of the acid with NaH and $(PhO)_2P(O)N_3$ gave the acyl azide.[22] Thermolysis of the acyl azide gave the unstable isocyanate. Employment of the literature reagent ($LiEt_3BH$)[22] for the conversion of this isocyanate to formamide **21** gave only over-reduction. Fortunately, $NaBH_4$ in *t*-BuOH/water reduced the isocyanate cleanly to the formamide **21**. We found that it was crucial to use *tert*-butyl alcohol as the solvent in this reduction, as use of ethanol led to substantial amounts of the derived urethane. The formamide **21** was the expected mixture of four geometric isomers on the ^1H NMR time scale (rt).

Dehydration of the formamide **22**[2a] gave the intermediate bis-silyloxy isonitrile. We were concerned about our ability to

(15) In fact, the alkylidene carbene derived from **12** inserted into both positions to give a 1:1 ratio of the desired cyclopentene and the byproduct dihydrofuran.

(16) Wrobel, J. E.; Ganem, B. *J. Org. Chem.* **1983**, *48*, 3761.

(17) Carreira, E. M.; Hastings, C. A.; Shepard, M. S.; Yerkey, L. A.; Millward, D. B. *J. Am. Chem. Soc.* **1994**, *116*, 6622.

(18) Villieras, J.; Perriot, P.; Normant, J. F. *Synthesis* **1979**, 502.

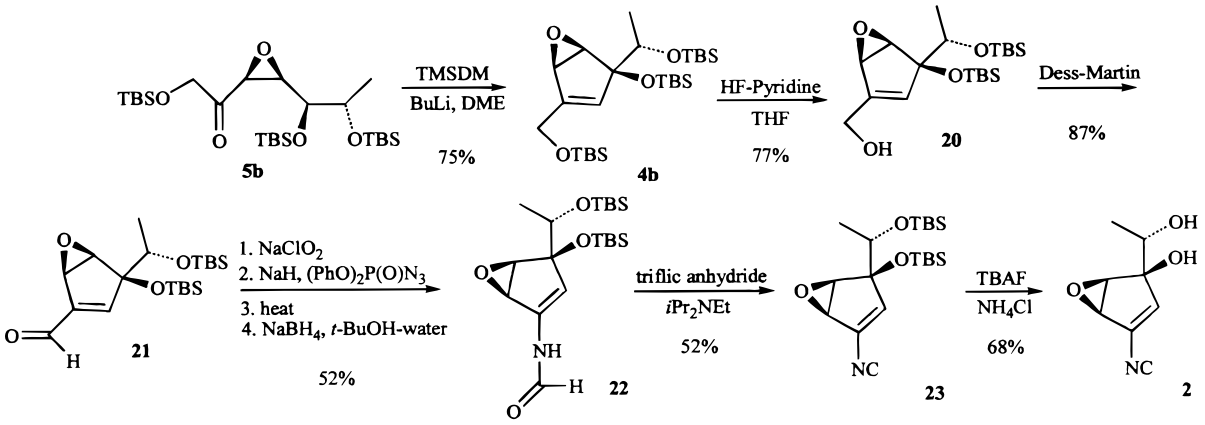
(19) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

(20) Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 9434.

(21) Isobe, M.; Ichikawa, Y.; Bai, D.; Masaki, H.; Goto, T. *Tetrahedron* **1987**, *43*, 4767.

(22) Chenera, B.; Chung, C.; Hart, D. J.; Lai, C. *J. Org. Chem.* **1992**, *57*, 2018.

Scheme 5



deprotect this to the very sensitive natural product. Fortunately, the combination of TBAF in THF buffered with solid NH_4Cl recently developed in our laboratory[23] effected smooth desilylation to give the natural product isonitrin B (**2**). The synthetic **2** exhibited identical properties to those reported for the natural substance (^{1}H NMR, GC-MS, IR; $[\alpha]_D = -92.2°$ (lit. $= -89.9$).[24]

We have completed the first synthesis of the natural enantiomer of (−)-isonitrin B (**2**), confirming the assigned absolute configuration. Isonitrile **23**, a similar intermediate to that in the trichoviridin synthesis of Baldwin, should be convertible to trichoviridin (**3**) in four steps following his procedures.

Conclusion

It is encouraging that the strained bicyclic skeleton of **2** can be formed directly by alkylidene carbene insertion. The approach outlined here should pave the way for the construction of other members of this family of isonitrile antibiotics.

Experimental Section[25]

(3*S*,4*S*)−(*E*)-1,1-Dibromo-3,4-(*tert*-butyldimethylsiloxy)pentene (15). To a flask containing AD-mix-α (37.1 g) in *tert*-butyl alcohol (130 mL) and water (130 mL) at room temperature was added methanesulfonamide (2.5 g, 26.5 mmol). The mixture was cooled to 0 °C, then (*E*)-1,1-dibromo-*trans*-1,3-pentadiene (**5**) (6.0 g, 26.5 mmol) was added at once, and the heterogeneous slurry was stirred vigorously at 0 °C for 24 h. Solid sodium sulfite (40 g) was added at 0 °C, and the mixture was allowed to warm to room temperature and stirred for 1 h. The mixture was extracted with EtOAc (3 × 100 mL), and the layers were separated. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to give the diol (4.7 g, 18.0 mmol, 68% yield) as a pale yellow oil: ee = 73% (HPLC column Chiralcel OD; injection amount 30 μL; sample concentration 2 mg of diol/1 mL of mobile phase solvent; mobile phase hexane/2-propanol (95/5 v/v); flow rate 1 mL/min). This was further crystallized from 95% EtOH (20 mg/8 mL) to give a white crystalline compound: ee = 92%, TLC R_f (40% MTBE/petroleum ether) = 0.28; ^{1}H NMR δ 6.49 (d, J = 8.5 Hz, 1H), 4.11 (t, J = 7.5 Hz, 1H), 3.82 (bs, 1H), 3.74 (m, 1H), 3.45 (bs, 1H), 1.23 (d, J = 6.4 Hz, 3H); ^{13}C NMR δ down 137.4, 76.7, 69.8, 18.7; up 93.2; IR (cm^{-1}) 3361, 2976, 2931, 1618, 1375, 1264, 1134, 1055; FAB MS (*m*/*z*) 55 (51), 105 (31), 107 (35), 135 (100), 137 (88), 215 (38); FAB HRMS calcd for $Br_2C_5H_8O_2Na$ 282.8789, found 282.8768; $[\alpha]_D$ −8.8 (*c* 2.0, $CHCl_3$).

To a solution of diol (1.1 g, 4.2 mmol) in DMF (22 mL) were added imidazole (3.0 g, 42.3 mmol), DMAP (321 mg, 2.6 mmol), and *tert*-butyldimethylsilyl chloride (3.3 g, 21.9 mmol). The mixture maintained at reflux (bath = 80 °C) for 3 h and then was quenched with 20 mL of water at room temperature. EtOAc (2 × 20 mL) was added, and the layers were separated. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to afford dibromide **15** (1.88 g, 3.85 mmol, 91% yield) as a clear oil, TLC R_f (100% petroleum ether) = 0.38; ^{1}H NMR δ 6.39 (d, J = 8.6 Hz, 1H), 4.18 (m, 1H), 3.75 (m, 1H), 1.11 (d, J = 6.3 Hz, 3H), 1.11 (m, 18H), 0.03 (m, 12H); ^{13}C NMR δ down 138.8, 76.7, 71.0, 25.9, 25.8, 25.7, 18.4, −4.5, −4.6, −4.7, −4.8; up 89.8, 18.1; IR (cm^{-1}) 2928, 2858, 1616, 1472, 1362, 1255, 1108; FAB MS (*m*/*z*) 57 (23), 73 (85), 75 (22), 147 (100), 159 (68), 189 (24); FAB HRMS calcd for $Br_2C_{17}H_{36}O_2Si_2Na$ 509.0556, found 509.0518; $[\alpha]_D$ −7.0 (*c* 2.1, $CHCl_3$). Anal. Calcd for $Br_2C_{17}H_{36}O_2Si_2$: C, 41.80; H, 7.43. Found: C, 41.87; H, 7.69.

(2*R*,5*S*,6*S*)-1,5,6-(Tris-*tert*-butyldimethylsiloxy)hept-3-yn-2-ol and (2*S*,5*S*,6*S*)-1,5,6-(Tris-*tert*-butyldimethylsiloxy)hept-3-yn-2-ol (17). *n*-BuLi (3.5 mL of 2.21 M in hexane, 7.6 mmol) was added dropwise at −78 °C to a solution of dibromide **15** (1.2 g, 2.5 mmol) in 16 mL of THF. After 5 min of stirring at −78 °C, the mixture was allowed to warm to −35 °C for 20 min. The siloxy aldehyde (0.87 g, 5.0 mmol) in 1.0 mL of THF was added to the above mixture at 0 °C at once. After 5 min of stirring at 0 °C, the mixture was quenched by the addition of 20 mL of water and extracted with EtOAc (3 × 20 mL). The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to give alkyne **17** (1.1 g, 2.1 mmol, 84% yield) as a pale yellow oil: TLC R_f (10% MTBE/petroleum ether) = 0.60; ^{1}H NMR δ 4.39 (m, 1H), 4.19 (m, 1H), 3.72 (m, 2H), 3.58 (m, 1H), 1.16 (d, J = 4.8 Hz, 1H), 1.16 (d, J = 6.1 Hz, 3H), 0.88 (m, 27 H), 0.06 (m, 18 H); ^{13}C NMR δ down 71.4, 68.2, 63.2, 25.8, 19.0, −4.5, −4.6, −4.7, −5.3; up 85.0, 83.0, 67.0, 18.3, 18.2, 18.1; IR (cm^{-1}) 3454, 2957, 2859, 1743, 1362, 1257, 1119; MS (*m*/*z*) 73 (98), 75 (38), 115 (33), 147 (68), 150 (25), 159 (100), 313 (73); HRMS calcd for $C_{25}H_{54}O_4Si_3$ 502.3305, found 502.3330; $[\alpha]_D$ −7.7 (*c* 0.9, $CHCl_3$).

(2*R*,5*S*,6*S*)-1,5,6-(*tert*-Butyldimethylsiloxy)hept-3-en-2-ol (18a) and (2*S*,5*S*,6*S*)-1,5,6-(*tert*-butyldimethylsiloxy)hept-3-en-2-ol (18b). Sodium borohydride (215 mg, 5.7 mmol) was added to a suspension of $Ni(OAc)_2 \cdot 4H_2O$ (900 mg, 3.6 mmol) in 7 mL of ethanol at 0 °C. The black suspension was vacuun/refilled for three times. Then, 2 mL of ethylenediamine and the alkyne **17** (1.14 g, 2.27 mmol) in 1.5 mL of ethanol were added sequentially. The black suspension was stirred vigorously under an atmosphere of hydrogen at room temperature for 48 h. The reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated in vacuo. The residue was chromatographed to give the desired alkene **18a** (444 mg, 0.88 mmol) and its diastereomer **18b** (440 mg, 0.87 mmol, 77% combined yield of **18a** and **18b**), as clear pale yellow oils.

For **18a**: TLC R_f (1:4:6 toluene:CH_2Cl_2:petroleum ether) = 0.44; ^{1}H NMR δ 5.46 (m, 2H), 4.45 (m, 1H), 4.38 (m, 1H), 3.73 (m, 1H), 3.60 (m, 1H), 3.41 (m, 1H), 2.69 (d, J = 3.0 Hz, 1H), 1.04 (d, J = 6.2 Hz, 3H), 0.85 (m, 27 H), 0.03 (m, 18 H); ^{13}C NMR δ down 133.2,

(23) Taber, D. F.; Kanai, K. *Tetrahedron* **1998**, *54*, 11767.

(24) The ^{1}H and ^{13}C NMR spectra were recorded in CD_2Cl_2, as reported in conjuction with the original isolation. Isonitrin B (**2**) is not stable to $CDCl_3$.

(25) For general experimental procedures, see: Taber, D. F.; Houze, J. B. *J. Org. Chem.* **1994**, *59*, 4004.

129.2, 72.6, 72.4, 68.2, 26.0, 25.9, 18.0, −4.4, −4.8, −5.3, −5.4; up 67.0, 18.3; IR (cm^{-1}) 3432, 2956, 2858, 1473, 1362, 1257, 1101; FAB MS (*m*/*z*) 303 (43), 315 (100), 327 (39), 355 (93), 373 (26), 505 (36); FAB HRMS calcd for $C_{25}H_{56}O_4Si_3Na$ 527.3403, found 527.3384; $[\alpha]_D$ −38.4 (*c* 1.4, $CHCl_3$).

For **18b**: TLC R_f (1:4:6 toluene:CH_2Cl_2:petroleum ether) = 0.41; ^1H NMR δ 5.64−5.40 (m, 2H), 4.45 (m, 1H), 4.33 (m, 1H), 3.80 (m, 1H), 3.58 (m, 2H), 2.88 (d, J = 2.3 Hz, 1H), 1.07 (d, J = 6.3 Hz, 3H), 0.87 (m, 27H), 0.03 (m, 18H); ^{13}C NMR δ down 133.7, 131.4, 72.8, 72.5, 67.7, 26.1, 25.9, 25.8, 25.7, 17.4, −4.4, −4.6, −4.7, −5.3, −5.4; up 66.6, 18.5, 18.3, 18.0; IR (cm^{-1}) 3407, 2930, 2862, 1466, 1256, 1091; FAB MS (*m*/*z*) 425 (5), 461 (100), 505 (21), 553 (M^+ + Na, 59); FAB HRMS calcd for $C_{25}H_{56}O_4Si_3Na$ 527.3385; found 527.3384; $[\alpha]_D$ −14.1 (*c* 1.2, $CHCl_3$).

Alkene 18b to Alkene 18a. To a solution of Dess−Martin periodinane (694 mg, 1.63 mmol) in 10 mL of CH_2Cl_2 was added alkene **18b** (687 mg, 1.36 mmol) in 2 mL of CH_2Cl_2. The mixture was stirred at room temperature for 3 h, and then 10 mL of 1:1 10% $Na_2S_2O_3$: saturated aqueous $NaHCO_3$ was added. The mixture was stirred until it turned clear. The layers were separated, and the mixture was partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. The combined organic extract was dried (Na_2SO_4) and concentrated to give the crude ketone (670 mg, 1.33 mmol) as a clear oil.

To the above crude ketone (670 mg, 1.33 mmol) in 7 mL of EtOH was added $NaBH_4$ (101 mg, 2.66 mmol) at room temperature. The reaction mixture was stirred at room temperature for 3 h; water (8 mL) was then added and stirring was continued for an additional 10 min. The resulting mixture was partitioned between EtOAc and water. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to give the desired alkene **18a** (275 mg, 0.54 mmol, 40% yield from **18b**) and its diastereomer **18b** (254 mg, 0.50 mmol, 37% yield from **18b**), each as a pale yellow oil.

Epoxide 19a and Epoxide 19b. To a flask containing alkene **18a** (1.09 g, 2.16 mmol) in 20 mL of CH_2Cl_2 was added *m*CPBA (50−60%, 1.20 g, 3.49 mmol) in 2 mL of CH_2Cl_2. The mixture was stirred at room temperature overnight and then was partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to give the desired epoxide **19b** (754 mg, 1.47 mmol, 67% yield) and its diastereomer **19a** (281 mg, 0.54 mmol, 25% yield), each as a pale yellow oil.

For **19b**: TLC R_f (8% MTBE/petroleum ether) = 0.50; ^1H NMR δ 3.84−3.67 (m, 5H), 3.11 (m, 2H), 2.50 (d, J = 6.2 Hz, 1H), 1.17 (d, J = 6.4 Hz, 3H), 0.85 (m, 27 H), 0.07 (m, 18 H); ^{13}C NMR δ down 74.0, 71.5, 68.1, 58.9, 57.5, 25.9, 25.8, 18.5, −4.3, −4.5, −4.6, −5.0, −5.4; up 65.3, 18.3, 18.1; IR (cm^{-1}) 3440, 2957, 2859, 1473, 1362, 1257, 1102; MS (*m*/*z*) 73 (100), 75 (35), 89 (19), 115 (19), 117 (19), 159 (39); HRMS calcd for $C_{25}H_{57}O_5Si_3$ 521.3556, found 521.3514; $[\alpha]_D$ −0.9 (*c* 0.8, $CHCl_3$). Anal. Calcd for $C_{25}H_{57}O_5Si_3$: C, 57.64; H, 10.83. Found: C, 57.94; H, 11.95.

For **19a**: TLC R_f (8% MTBE/petroleum ether) = 0.48; ^1H NMR δ 3.89 (m, 1H), 3.74 (m, 4H), 3.10 (m, 1H), 2.92 (m, 1H), 2.65 (d, J = 4.1 Hz, 1H), 1.20 (d, J = 4.1 Hz, 3H), 0.85 (m, 27H), 0.03 (m, 18H); ^{13}C NMR δ down 72.4, 70.3, 68.6, 56.7, 56.5, 25.8, 18.8, −4.3, −4.5, −4.8, −5.0, −5.4; up 65.2, 18.3, 18.1, 18.0; IR (cm^{-1}) 3440, 2958, 2858, 1474, 1361, 1259, 1116; FAB MS (*m*/*z*) 231 (46), 257 (38), 303 (100), 331 (33), 371 (22); FAB HRMS calcd for $C_{25}H_{56}O_5Si_3Na$ 543.3333, found 543.3333; $[\alpha]_D$ −23.7 (*c* 0.5, $CHCl_3$).

Ketone 5b. Alcohol **19b** (0.51 g, 0.97 mmol) in 1 mL of CH_2Cl_2 was added to a suspension of PCC mixture (1.26 g of 1:1:1 NaOAc:4A molecular sieve:PCC, ground together, 1.94 mmol) in 6 mL of CH_2Cl_2. The mixture was stirred at room temperature for 5 h; 10 mL of Et_2O was then added, and the mixture was filtered through a pad of Celite. The solid was washed with 3 × 5 mL of Et_2O. The filtrate was concentrated, and the brown residue was chromatographed to give the ketone **5b** (0.39 g, 0.76 mmol, 78% yield) as a clear oil: TLC R_f (8% MTBE/petroleum ether) = 0.58; ^1H NMR δ 4.36 (s, 2H), 3.83 (d, J = 4.5 Hz, 1H), 3.74−3.65 (m, 1H), 3.40−3.29 (m, 2H), 1.12 (d, J = 6.4 Hz, 3H), 1.00−0.83 (m, 27 H), 0.14−0.02 (m, 18 H); ^{13}C NMR δ down 73.4, 70.8, 60.3, 55.6, 26.0, 25.8, 18.8, −4.3, −4.5, −4.6, −5.0, −5.4, −5.5; up 203.6, 69.0, 18.3, 18.1; IR (cm^{-1}) 2956, 2858, 1735, 1473, 1362, 1257, 1097; MS (*m*/*z*) 73 (100), 75 (38), 115 (39), 131 (45), 147 (30), 159 (70); HRMS calcd for $C_{25}H_{54}O_5Si_3$ 518.3264, found 518.3279; $[\alpha]_D$ −15.1 (*c* 1.2, $CHCl_3$).

Cyclopentene 4b. Under nitrogen, *n*-BuLi (0.59 mL of 2.21 M in hexane, 1.30 mmol) was added dropwise over 5 min at −60 °C to (trimethylsilyl)diazomethane (0.72 mL, 2.0 M in hexane, 1.43 mmol) in DME (4 mL). After 5 min at −60 °C, the dry ice bath was removed, and the mixture was allowed to warm. Once it turned homogeneous (about 5 min), the reaction mixture was then cooled to −40 °C immediately, and ketone **5b** (338 mg, 0.65 mmol) in 1 mL of DME was added dropwise over 5 min. The solution was stirred at −30 to −40 °C for another 45 min and then warmed to room temperature over 2 h. The resulting mixture was partitioned between saturated aqueous NH_4Cl and EtOAc. The combined organic extract was dried (Na_2SO_4) and concentrated, and the residue was chromatographed to give the cyclopentene **4b** (253 mg, 0.49 mmol, 75% yield) as a clear oil: TLC R_f (8% MTBE/petroleum ether) = 0.66; ^1H NMR δ 5.29 (t, J = 2.0 Hz, 1H), 4.28 (ddd, J = 1.8 Hz, J = 4.8 Hz, J = 7.2 Hz, 2H), 3.65 (m, 2H), 3.53 (t, J = 2.7 Hz, 1H), 1.23 (d, J = 6.1 Hz, 3H), 0.89 (m, 27H), 0.06 (m, 18H); ^{13}C NMR δ down 133.3, 72.5, 56.9, 54.9, 25.9, 25.8, 17.7, −2.8, −3.0, −4.2, −4.8, −5.4; up 145.7, 85.8, 60.7, 18.4, 18.3, 18.0; IR (cm^{-1}) 2929, 2856, 1471, 1255, 1124; MS (*m*/*z*) 73 (100), 147 (51), 159 (29), 356 (29), 382 (35), 457 (24), 499 (26), 515 (27); HRMS calcd for $C_{26}H_{56}O_4Si_3$ 516.3471, found 516.3486; $[\alpha]_D$ −20.0 (*c* 1.2, $CHCl_3$).

Alcohol 20. To a solution of cyclopentene **4b** (97 mg, 0.19 mmol) in 7 mL of THF in a Nalgene tube was added 7.1 mL of freshly prepared, buffered pyridinium hydrofluoride (stock solution prepared from 2.4 g of Aldrich pyridinium hydrofluoride, 5 mL of pyridine, and 20 mL of THF). The reaction mixture was stirred at room temperature for 2.5 h, and then 10 mL of saturated aqueous $NaHCO_3$ was added slowly. After an additional 5 min, the layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated, and the residue was chromatographed to give the alcohol **20** (58 mg, 0.14 mmol, 77% yield) as a white solid: TLC R_f (40% MTBE/petroleum ether) = 0.40; ^1H NMR δ 5.36 (t, J = 2.0 Hz, 1H), 4.29 (dd, J = 2.1 Hz, J = 2.9 Hz, 2H), 3.65 (m, 3H), 1.58 (d, J = 5.9 Hz, 1H), 1.24 (d, J = 6.1 Hz, 3H), 0.85 (s, 9H), 0.84 (s, 9 H), 0.11 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H), −0.01 (s, 3H); ^{13}C NMR δ down 134.6, 72.4, 57.0, 54.7, 25.9, 25.7, 17.7, −2.8, −2.9, −4.1, −4.8; up 145.3, 85.8, 60.6, 18.4, 18.0; IR (cm^{-1}) 3380, 2929, 2857, 1252, 1121; MS (*m*/*z*) 73 (100), 75 (94), 119 (33), 159 (31), 242 (40); HRMS calcd for $C_{20}H_{40}O_4Si_2$ 400.2483, found 400.2465; $[\alpha]_D$ −18.9 (*c* 0.8, $CHCl_3$).

Aldehyde 21. To a solution of Dess−Martin periodinane (115 mg, 0.27 mmol) in 3 mL of CH_2Cl_2 was added alcohol **20** (90 mg, 0.22 mmol) in 1 mL of CH_2Cl_2. The mixture was stirred at room temperature for 10 min, and then 2 mL of 1:1 10% $Na_2S_2O_3$:saturated aqueous $NaHCO_3$ was added. The mixture was stirred until it turned clear. The layers were separated, and the mixture was partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to provide the aldehyde **21** (78 mg, 0.20 mmol, 87% yield) as a white solid: TLC R_f (5% MTBE/petroleum ether) = 0.42; ^1H NMR δ 9.73 (s, 1H), 6.39 (t, J = 2.2 Hz, 1H), 4.03 (t, J = 2.6 Hz, 1H), 3.76 (m, 2H), 1.29 (d, J = 6.3 Hz, 3H), 0.85 (s, 9H), 0.81 (s, 9H), 0.13 (s, 3H), 0.03 (s, 3H), 0.00 (s, 3H), −0.04 (s, 3H); ^{13}C NMR δ down 188.0, 156.1, 72.1, 53.8, 53.6, 25.8, 25.7, 17.8, −0.01, −3.1, −4.1, −4.8; up 146.3, 86.4, 18.4, 17.9; IR (cm^{-1}) 2931, 2858, 1691, 1473, 1372, 1254, 1202, 1125; MS (*m*/*z*) 73 (100), 75 (22), 103 (16), 115 (21), 147 (32), 159 (50); HRMS calcd for $C_{20}H_{38}O_4Si_2$ 398.2329, found 398.2309. $[\alpha]_D$ −70.6 (*c* 0.5, $CHCl_3$).

Formamide 22. To a solution of the above aldehyde **21** (72 mg, 0.18 mmol), 2-methyl-2-butene (0.41 mL of 2.0 M in THF, 0.81 mmol) and $NaH_2PO_4 \cdot H_2O$ (25 mg, 0.18 mmol) dissolved in a mixture of 3 mL of *t*-BuOH and 0.9 mL of water was added $NaClO_2$ (80%, 69 mg, 0.61 mmol) portionwise over 2 min. The yellow mixture was stirred at room temperature for 1 h, and then the reaction was quenched with 3 mL of freshly prepared saturated aqueous $NaHSO_3$. The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 5 mL) at pH = 7.0. The combined organic extract was dried (Na_2SO_4)

and concentrated to give the crude acid (73 mg) as a white solid: TLC R_f (15% MeOH/CH_2Cl_2) = 0.33.

To a stirred solution of the above crude acid (73 mg) in 3 mL of dry THF at room temperature was added NaH (7.2 mg of 60% in mineral oil, 0.18 mmol). The reaction mixture was stirred for 10 min at room temperature and then cooled to 0 °C, and a solution of $(PhO)_2P(O)N_3$ (52 mg, 0.19 mmol) in 2 mL of THF was added in one portion. The mixture was stirred at 0 °C for 1 h and at room temperature for 6 h. The mixture was partitioned between Et_2O and water. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was eluted through 3 g of silica gel to afford the unstable acyl azide (55 mg, 0.13 mmol) as a clear oil: TLC R_f (5% MTBE/petroleum ether) = 0.62; IR (cm^{-1}) 2930, 2858, 2136, 1697, 1560, 1384, 1258.

The above acyl azide (55 mg, 0.13 mmol) in 1.5 mL of dry benzene was maintained at reflux until the TLC showed no starting material (about 1.75 h). The solution was then concentrated to give the unstable isocyanate as a thick clear oil: IR (cm^{-1}) 2948, 2860, 2262, 1488, 1366, 1113.

To a flask containing 1.5 mL of *t*-BuOH was added $NaBH_4$ (9.5 mg, 0.25 mmol), followed immediately by 0.3 mL of distilled water. After 15 s of stirring at room temperature, this mixture was added all at once to the flask containing the neat isocyanate. The resulting mixture was stirred at room temperature for 2 min; MeOH (2 mL) was then added, and stirring was continued for 5 an additional min. The mixture was concentrated in vacuo, and saturated aqueous Na_2HPO_4 (2 mL) was added. The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 2 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated, and the residue was chromatographed to give the formamide **22** (38 mg, 0.092 mmol, 52% yield from aldehyde **21**) as a clear oil, a 3:1 mixture of geometrical isomers by integration of selected peaks in the ^1H NMR spectrum of the mixture: TLC R_f (20% EtOAc/petroleum ether) = 0.36; ^1H NMR δ 8.53 (d, J = 11.4 Hz, 0.3H), 8.27 (d, J = 1.2 Hz, 0.7H), 7.20 (bs, 0.3H), 7.01 (bs, 0.7H), 5.59 (t, J = 2.3 Hz, 0.7H), 4.83 (t, J = 2.3 Hz, 0.3H), 3.66 (m, 3H), 1.26 (d, J = 6.2 Hz, 2.1H), 1.25 (d, J = 6.3 Hz, 0.9H), 0.84 (m, 18H), 0.10 (m, 12H); ^{13}C NMR δ down 158.4, 157.5, 120.1, 115.5, 72.7, 57.2, 53.6, 25.9, 25.8, 25.7, 18.4, −2.9, −3.0, −4.2, −4.8; up 138.5, 136.6, 114.6, 85.1, 18.4, 17.9; IR (cm^{-1}) 3320, 2956, 2858, 1684, 1560, 1473, 1256, 1116; MS (*m*/*z*) 57 (24), 73 (100), 75 (42), 147 (18), 159 (22), 254 (23); HRMS calcd for $C_{20}H_{39}NO_4Si_2$ 413.2400, found 413.2418; $[\alpha]_D$ −16.4 (*c* 1.0, $CHCl_3$).

Isonitrile 23. To a stirred solution of dry formamide (38 mg, 0.092 mmol) in CH_2Cl_2 (6 mL) under nitrogen at −78 °C was added dry diisopropylethylamine (0.096 mL, 0.55 mmol) followed by triflic anhydride (39 mg, 0.14 mmol) in 1 mL of CH_2Cl_2. The solution was stirred at −78 °C for 40 min, and the reaction was then quenched by the addition of saturated aqueous $NaHCO_3$ (4 mL) at −78 °C. The mixture was allowed to warm to room temperature, the layers were separated, and the mixture was partitioned between $CH_2Cl_2$and saturated aqueous $NaHCO_3$. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographied to provide the isonitrile **23** (19 mg, 0.048 mmol, 52% yield) as a white solid: TLC R_f (5% MTBE/petroleum ether) = 0.53; ^1H NMR δ 5.64 (t, J = 2.3 Hz, 1H), 3.71 (m, 3H), 1.25 (d, J = 6.2 Hz, 3H), 0.85 (s, 9H), 0.84 (s, 9H), 0.12 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.00 (s, 3H); ^{13}C NMR δ 170.2, 137.8, 128.9, 84.2, 71.9, 57.3, 53.5, 25.5, 25.4, 18.2, 17.7, 17.2, −3.3, −3.5, −4.6, −5.3; IR (cm^{-1}) 2956, 2859, 2115, 1473, 1259, 1120; MS (*m*/*z*) 57 (29), 73 (100), 75 (22), 115 (25), 147 (51), 159 (64); HRMS calcd for $C_{20}H_{37}NO_3Si_2$ 395.2400 found 338.3315 + C_4H_8; $[\alpha]_D$ −18.1 (*c* 0.5, $CHCl_3$).

Isonitrin B (2). To a stirred solution of isonitrile **23** (19 mg, 0.048 mmol) in dry THF (5 mL) at 0 °C was added tetrabutylammonium fluoride (0.11 mL of 1.0 M in THF, 0.11 mmol) and solid NH_4Cl (13 mg, 0.24 mmol). The reaction mixture was stirred at 0 °C for 30 min, 5 mL of Et_2O was then added, and the mixture was filtered through 0.5 g of silica gel. The filtrate was concentrated in vacuo, and the residue was chromatographed to give isonitrin B (**2**) (5.5 mg, 0.033 mmol, 68% yield) as a white solid: TLC R_f (10% THF/CH_2Cl_2) = 0.34; ^1H NMR δ 5.90 (t, J = 2.2 Hz, 1H), 3.88−3.82 (m, 2H), 3.78 (t, J = 2.4 Hz, 1H), 2.47 (s, 1H), 2.36 (d, J = 5.9 Hz, 1H), 1.19 (d, J = 6.5 Hz, 3H); ^{13}C NMR δ down 171.5, 135.3, 130.5, 82.4, 69.6, 57.4, 55.5, 16.9; IR (cm^{-1}) 3410, 2111, 1627, 1380, 1103; MS (*m*/*z*) 58 (23), 67 (20), 68 (51), 81 (21), 86 (100), 96 (39), 122 (23); HRMS calcd for $C_8H_9NO_3$ 167.0579, found 167.0582; $[\alpha]_D$ −92.2 (*c* 0.2, MeOH).

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Supporting Information Available: Additional experimental procedures, ^1H and ^{13}C spectra for compounds **2**, **4b**, **5b**, **15**, and **17**−**23**, full crystallographic details including crystal data and structure refinement, atomic coordinates, bond lengths and angles, and anisotropic displacement coefficients (39 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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